

Impairment of Filgrastim-Induced Stem Cell Mobilization after Prior Lenalidomide in Patients with Multiple Myeloma

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Lenalidomide is an agent that has shown great activity in patients with multiple myeloma (MM). However, studies have suggested that this drug negatively affects subsequent stem cell collection. To investigate whether lenalidomide impairs stem cell mobilization and collection, we reviewed data for patients with MM who underwent mobilization with filgrastim. Predictors of mobilization failure were evaluated using logistic regression analysis. In 26 (9%) of 302 myeloma patients, stem cell mobilization failed. Mobilization failed in 25% of patients who had previously received lenalidomide, compared with 4% of patients who had not received lenalidomide ($P < .001$). In a multivariate analysis, prior lenalidomide use (odds ratio: 5.9; 95% confidence interval [CI]: 2.4-14.3) and mobilization more than 1 year after diagnosis (odds ratio: 4.6; 95% CI: 1.9-11.1) were significantly associated with failed mobilization. Twenty-one of 26 patients in whom mobilization with filgrastim failed underwent remobilization with chemotherapy and filgrastim; in 18 (86%) of these 21 patients, stem cells were successfully mobilized and collected. In patients with multiple myeloma, prior lenalidomide therapy is associated with failure of stem cell mobilization with filgrastim. Remobilization with chemotherapy and filgrastim is usually successful in these patients.

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INTRODUCTION

Thalidomide, bortezomib, and lenalidomide are changing therapeutic paradigms in patients with multiple myeloma (MM) [1,2]. Used as salvage therapy, these agents have been highly effective in increasing response rates, event-free survival (EFS), and overall survival (OS) when standard therapies have failed [3-13]. Increasingly, these agents are being used as frontline therapies [14-18]. As initial therapy, Thalidomide

plus dexamethasone has proved to be superior to dexamethasone alone [16]. How these agents integrate with autologous stem cell transplantation (ASCT), a standard therapy that improves survival [19-22], is being studied extensively, especially with regard to their impact on stem cell collection, a necessary step in the transplantation process.

Stem cell mobilization, or release of hematopoietic stem cells from the bone marrow (BM) to the peripheral blood (PB) in response to cytokines or chemotherapy, is dependent on several factors. These include patient age, BM reserve, mobilizing regimen, and prior therapy [23-25]. Melphalan (Mel) use before stem cell collection has been associated with poor stem cell yield and mobilization failure [26]; therefore, it is not used as first-line therapy in patients who are candidates for autologous transplantation. Recently, concern has been raised about lenalidomide's tendency to similarly decrease stem cell yield and increase the mobilization failure rate [27-29]. Lenalidomide is myelosuppressive and alters stromal milieu, and may indeed suppress stem cell mobilization. To confirm the hypothesis that lenalidomide impairs stem cell

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mobilization, we studied the impact of prior lenalidomide use on stem cell mobilization and collection with filgrastim. We also looked at other factors besides prior lenalidomide that affected mobilization outcome, and whether remobilization attempts were successful in cases in which the first mobilization attempt failed.

PATIENTS AND METHODS

Included in this retrospective study were all patients with MM referred to the Department of Stem Cell Transplantation and Cellular Therapy at The University of Texas M.D. Anderson Cancer Center, between January 2005 and October 2007, who underwent stem cell mobilization with filgrastim. Detailed information about demographics, disease isotype, stage, prior treatment, interval from diagnosis, premobilization blood counts, and bone marrow cellularity was obtained from the departmental database and chart review. Data were updated and analyzed in January 2008. Permission for this retrospective review was obtained from the institutional review board.

Of the 354 patients with MM mobilized during this period, 302 patients underwent mobilization with filgrastim and are included in this study. Excluded were 52 patients who underwent mobilization with alternative strategies: Chemotherapy and filgrastim ($n = 40$), plerixafor plus filgrastim ($n = 4$), and pegfilgrastim ($n = 8$). Chemotherapy was used at the discretion of the treating physician if the patient had disease that was unresponsive to previous therapy; 2 of 40 patients received cyclophosphamide (Cy), and the remaining 38 of 40 received CVAD (Cy, vincristine, doxorubicin, dexamethasone).

Leukapheresis

Patients received filgrastim at a dose of $10 \mu\text{g/kg/day}$ until completion of stem cell collection. Dose was adjusted at the discretion of the apheresis physician if the PB CD34 count or stem cell yield were suboptimal. Counts of PB circulating CD34⁺ progenitor cells were checked, and leukapheresis was started when the PB CD34⁺ count exceeded $0.010 \times 10^9/\text{L}$. All patients underwent leukapheresis using the COBE Spectra cell separator (COBE BCT, Inc., Lakewood, CO). Three times the estimated blood volume was processed during each collection. Standard citrate dextrose solution was used as an anticoagulant. Daily leukapheresis was performed until the target cell doses reached at least 6×10^6 CD34⁺ cells/kg for patients who were to undergo tandem transplantation and reached at least $3 \times 10^6/\text{kg}$ for patients who were to undergo a single transplantation procedure.

If the collected CD34⁺ cell dose was $<0.5 \times 10^6/\text{kg/day}$ on 2 consecutive days, the apheresis was stopped.

Statistical Analysis

Mobilization failure was defined as the inability to collect at least 2×10^6 CD34⁺ cells/kg in 4 leukapheresis procedures. Risk factors predicting mobilization failure were determined using logistic regression analysis. Factors studied in univariate analysis included age, number of prior treatment regimens, prior radiation therapy, interval between diagnosis and mobilization, white cell count, platelet count, BM cellularity, and prior lenalidomide treatment. Factors significant at a value of $P = .05$ or less were evaluated in a multivariate model.

RESULTS

Patient Characteristics

During the study period, 302 patients with MM underwent stem cell mobilization with filgrastim at our institution. Their median age was 58.5 years (range: 31-76 years). There were 185 men and 117 women. The majority of patients, 186 (62%), had received only 1 previous treatment regimen. Likewise, a majority of patients, 237 (78%), underwent mobilization within 12 months of diagnosis (Table 1). Lenalidomide was stopped at a median of 17.5 days (range: 1-211 days) prior to initiation of filgrastim for mobilization.

Mobilization Failures

In 26 (9%) of 302 patients, mobilization of stem cells failed. Significant predictors of mobilization failure on univariate analysis (Table 2) included more than 1 prior chemotherapy regimens ($P = .004$), an interval of more than 1 year after diagnosis of MM ($P < .001$), prior use of lenalidomide ($P < .001$), and transplants received in the year 2007 ($P = .02$). The failure rate (Figure 1) significantly increased in 2007 (14%) compared with rates in 2006 (5%) and 2005 (7%).

In a multivariate analysis evaluating the independent effects of these factors, only, prior lenalidomide use and stem cell mobilization more than 1 year after diagnosis of MM remained significant ($P < .001$), with odds ratios of 5.9 (95% confidence interval [CI], 2.4-14.3) and 4.6 (95% CI, 1.9-11.1), respectively (Table 2).

It is noteworthy that the year was no longer significant on multivariate analysis. This was likely because higher proportion of patients in 2007 had pretransplant lenalidomide compared with previous years; 45% of 98 patients seen in 2007 had received premobilization lenalidomide compared to 11% of 204 patients in previous years.

Table 1. Patient Characteristics (n = 302)

Characteristic	Number (%)
Age	
Median (range)	58.5 (38-76)
Sex	
Men	185 (61)
Women	117 (39)
Isotype	
IgG	177 (59)
IgA	63 (21)
Light chain only	47 (15)
Other (IgD, IgM, Nonsecretory)	15 (5)
Durie-Salmon stage at diagnosis	
I	59 (20)
II	127 (42)
III	103 (34)
Unknown	13 (4)
No. of previous treatment regimens	
I	186 (62)
>1	115 (38)
Interval from diagnosis to mobilization	
≤12 months	237 (78)
>12 months	65 (22)
Prior lenalidomide	
Yes	64 (21)
No	238 (79)

Subgroup Analysis

We performed a univariate subgroup analysis to identify patients at high risk of mobilization failure among those who received and those who did not receive lenalidomide. The interval between diagnosis and mobilization was the only significant predictor of failure in both subgroups. In addition, in patients who were previously treated with lenalidomide, >3 cycles of lenalidomide ($P = .001$), and >1 prior treatment regimen ($P = .04$) were associated with significantly higher risk. Mobilization failed in 78% of patients (7 of 9) who received >3 cycles of lenalidomide, compared with 16% of patients (9 of 55) who received 1 to 3 cycles of lenalidomide. It is noteworthy that the interval between the last day of lenalidomide therapy and filgrastim initiation did not significantly affect the success rate of stem cell mobilization. In addition, our data showed a trend for higher risk of failure for older patients ($P = .05$) who had received lenalidomide. Because of sample size limitations we could not perform a multivariate analysis to evaluate the independent effects of the interval since diagnosis, number of prior chemotherapy regimens, number of lenalidomide cycles, and age in the subgroup of patients who had received lenalidomide.

Remobilization

The majority of patients in whom mobilization failed, including those who received lenalidomide, successfully underwent remobilization with chemotherapy. Remobilization with chemotherapy and filgrastim was attempted in 21 of 26 patients for whom mobilization failed on the first attempt. Chemotherapy

regimens used included CVAD in 16 patients, Cy alone in 4 patients, and ifosfamide plus etoposide in 1 patient. Remobilization was successful in 18 (86%) of 21 patients; a median of 7×10^6 CD34⁺ cells/kg (range: $2.2\text{--}15 \times 10^6$ CD34⁺ cells/kg) was collected. This group included 10 (77%) of 13 patients who had previously received lenalidomide. All patients underwent autologous transplantation. Times to neutrophil and platelet engraftment were similar to those for the patients whose stem cells mobilized on the first attempt with filgrastim alone (data not shown). Two patients for whom $<2 \times 10^6$ CD34⁺ cells/kg were collected in 4 leukapheresis procedures underwent additional leukapheresis, and adequate doses of stem cells were collected after a total of 7 procedures in 1 patient and 8 procedures in the other. One patient underwent BM harvest. Repeat mobilization was not attempted in 2 patients.

Outcome of Patients Mobilized with Alternative Strategies

Thirty-nine of 40 patients given chemotherapy, and filgrastim were successfully mobilized, with a median yield of 13.2×10^6 CD34⁺ cells/kg (range: $2.1\text{--}70 \times 10^6$ CD34⁺ cells/kg). This included 12 patients who had previously received lenalidomide. One patient died prior to stem cell collection. All 4 patients who received plerixafor and filgrastim and 7 of 8 patients mobilized with Peg filgrastim were successfully collected; none of these 12 patients had received lenalidomide previously.

DISCUSSION

In this study, we suggest that lenalidomide use before transplantation impairs stem cell mobilization in response to filgrastim, but this effect is overcome by using chemotherapy and filgrastim. Mobilization with filgrastim failed in 25% of patients who had previously received lenalidomide, compared with 4% of patients who had not. In the majority of these patients (77%), remobilization with chemotherapy and filgrastim was successful, and these patients could successfully undergo ASCT.

Although our study is limited by its retrospective nature, several lines of reasoning support our conclusions. It could be argued that biases inherent in this design may explain our findings and that patients who received lenalidomide had advanced disease, and therefore were more susceptible to mobilization failure. However, this conclusion was not supported by the persistence of a significant lenalidomide effect after adjusting for the number of prior chemotherapy regimens in multivariate analysis. Among patients who had previously received only 1 chemotherapy regimen, a significantly higher mobilization failure

Table 2. Risk Factors Predicting Mobilization Failure*

	Univariate Analysis						Multivariate Analysis		
	N	N failed	% failed	OR	95% CI	P	OR	95% CI	P
Total	302	26	9%						
Age									
≤60 years	171	11	6%						
>60 years	131	15	11%	1.9	0.8-4.2	.13			
Prior chemo regimens									
≤1	186	9	5%						
>1	115	17	15%	3.4	1.5-7.9	.004			
Previous radiation									
Yes	90	9	10%	1.3	0.5-2.9	.6			
No	212	17	8%						
Interval between diagnosis and mobilization									
≤12 months	237	11	5%						
>12 months	65	15	23%	6.1	2.7-14	<.001	4.6	1.9-11.1	.001
White blood cell count ($\times 10^9$ /Liter)									
≤4	41	6	15%						
>4	260	20	8%	0.5	0.2-1.3	.15			
≤5.7 (median)	152	17	11%						
>5.7	149	9	6%	0.5	0.2-1.2	.1			
Platelet count ($\times 10^9$ /Liter)									
≤262 (median)	150	17	11%						
>262	151	9	6%	0.5	0.2-1.1	.1			
≤150	24	3	12%						
>150	277	23	8%	0.6	0.2-2.3	.5			
Cellularity									
≤30%	137	11	8%						
>30%	164	14	8%	1.1	0.5-2.4	.9			
≤35% (median)	159	13	8%						
>35%	142	12	8%	1	0.5-2.3	.9			
Prior lenalidomide									
No	238	10	4%						
Yes	64	16	25%	7.6	3.2-18	<.001	5.9	2.4-14.3	<.001
Year									
2005	67	5	7%						
2006	137	7	5%						
2007	98	14	14%	2.7	1.2-6	.02			

*Totals vary because of unknown values of some characteristics for 1 patient.

rate was seen in patients who received lenalidomide as part of that regimen (13%) than was seen in patients who had not received lenalidomide (3%). In fact, higher failure rates were seen in all subgroups of patients who received lenalidomide (Table 3). Moreover, the higher the number of courses of lenalidomide, the higher the failure rate; the failure rate was 78% in patients who had more than 3 courses of lenalidomide, compared with 16% in patients who received 3 courses or less.

Further supporting our findings are other reports of lower stem cell yields and increased mobilization failure rates in patients who had received prior lenalidomide [27-29]. Kumar et al. [27] reported a significant decrease in stem cell yield in patients who had been previously treated with lenalidomide compared with those who had not received it beforehand; moreover, among all patients who underwent mobilization with filgrastim, stem cells could not be collected in 3 (7%) of 43 patients who had previously received lenalidomide, compared with only 2 (1%) of 199 who had not received lenalidomide. All 3 lenalidomide-treated patients in whom mobilization failed had received

more than 6 months of this agent. Although confirming the trend of impaired stem cell mobilization after lenalidomide, the study of Kumar and colleagues [27] had a lower failure rate than did our study, possibly because Kumar et al. included only patients who were within 12 months of diagnosis. In our study, an interval

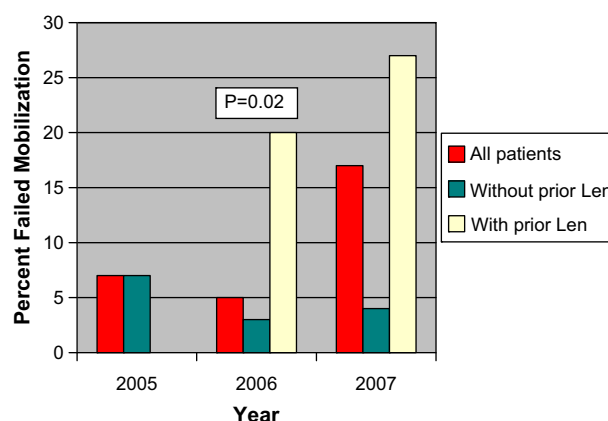


Figure 1. Mobilization failure rate by calendar year with and without prior lenalidomide (len). (No patient received lenalidomide in 2005.)

Table 3. Risk Factors Predicting Mobilization Failure in Patients Who Received and Those Who Did Not Receive Lenalidomide

	Lenalidomide Used				Lenalidomide Not Used			
	N	N Failed	% Failed	P	N	N Failed	% Failed	P
Age	64	16	25%		238	10	4%	
≤60 years	34	5	15%		137	6	4%	
>60 years	30	11	37%	.05	101	4	4%	.9
Prior chemo regimens								
≤1	31	4	13%		155	5	3%	
>1	33	12	36%	.04	82	5	6%	.3
Previous radiation								
Yes	24	5	21%		66	4	6%	
No	40	11	28%	.5	172	6	3%	.4
Interval between diagnosis and mobilization								
≤12 months	40	6	15%		197	5	3%	
>12 months	24	10	42%	.02	41	5	12%	.01
White blood cell count ($\times 10^9/\text{Liter}$)								
≤4	14	3	21%		27	3	11%	
>4	50	13	26%	.7	210	7	3%	.07
≤5.7 (median)	38	9	24%		114	8	7%	
>5.7	26	7	27%	.8	123	2	2%	.06
Platelet count ($\times 10^9/\text{Liter}$)								
≤262 (median)	36	11	31%		114	6	5%	
>262	28	5	18%	.2	123	4	3%	.4
≤150	8	2	25%		16	1	6%	
>150	56	14	25%	.9	221	9	4%	.7
Cellularity								
≤30%	27	6	22%		110	5	5%	
>30%	36	9	25%	.8	128	5	4%	.8
≤35% (med)	32	8	25%		127	5	4%	
>35%	31	7	23%	.8	111	5	5%	.8
Lenalidomide cycles								
1-3	55	9	16%		NA	NA	NA	
>3	9	7	78%	.001	NA	NA	NA	
Interval between stopping lenalidomide and mobilization								
≤9 days	18	5	28%		NA	NA	NA	
10-17 days	15	4	27%	.9	NA	NA	NA	
18-46 days	13	2	15%	.4	NA	NA	NA	
>46 days	17	4	24%	.8				

of >12 months between diagnosis of myeloma and collection of stem cells was a significant ($P < .001$) factor in predicting mobilization failure, a finding that has previously been documented as well [25].

Results of 2 other small case series [28,29] are in agreement with our findings. The first showed a mobilization failure rate of 45% in 20 lenalidomide-treated patients, compared with a rate of 7% in 41 patients who had not received lenalidomide. The second study showed a failure rate of 43% in 28 patients previously treated with lenalidomide. As in our study described here, stem cell remobilization in these patients was successfully induced with chemotherapy and filgrastim. The failure rate of 43%-45% observed in these studies is higher than the rate of 25% observed in the current study. It is possible that this may be because of differing patient characteristics. But it is also possible that because of the design of our study, we may have underestimated the incidence of mobilization failure. Patients were mobilized with filgrastim or chemotherapy at the discretion of their treating

physicians. Patients with high disease burden who had failed previous treatments were more likely to be mobilized with chemotherapy. Likewise, the realization of increased failure rate with filgrastim may have prompted upfront use of chemotherapy to mobilize stem cells in some of the patients who had previously received lenalidomide in the later period of the study.

Our study includes a large number of patients who were treated similarly at a single institution over a short period of time, so it provides the necessary power for identifying potential risk factors for mobilization failure. What this study does not do is provide a reason or a mechanism that explains the effect of lenalidomide on stem cell trafficking.

The role of prior Mel therapy in impairing subsequent stem cell collection has been well known, and frontline use of this agent is discouraged in patients who are suitable candidates for autologous transplantation [26]. The implications of this finding for lenalidomide are more uncertain, particularly because it is such an active agent, with a response rate of more than 90%

[17]. It has been recommended that stem cells should be collected within 6 months of starting lenalidomide [27]. Our data, however, indicate that the failure rate is very high (78%) if patients have received >3 cycles of this therapy. Mobilization with chemotherapy and filgrastim rather than filgrastim alone might be considered in patients receiving >3 cycles of lenalidomide prior to mobilization. Certainly, for patients in whom a first mobilization attempt with filgrastim fails, it would be reasonable to make a second mobilization attempt with chemotherapy and filgrastim, a strategy that was successful in more than three-quarters of our patients. The impact of newer mobilizing agents such as plerixafor for initial mobilization or remobilization in patients who have previously received lenalidomide is uncertain and needs to be studied.

To conclude, lenalidomide hampers subsequent stem cell mobilization and collection with filgrastim, and remobilization with chemotherapy and filgrastim is successful in most patients in whom stem cell mobilization with filgrastim alone has failed. The mechanism for this effect largely remains speculative and will certainly be a subject of further studies. This study does, however, have significant implications for how we should integrate this highly effective drug within our therapeutic armamentarium against MM.

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